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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/766,944	01/22/2001	Andrew R. Marks	61136/JPW/ADM/BJA	3387

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EXAMINER	
HARRIS, ALANA M	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/766,944	MARKS ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-6 and 19-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-6 and 19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments and Arguments

1. Claims 3-6 and 19-21 are pending.

Claims 6, 19 and 21 have been amended.

Claims 1, 2 and 7-18 have been cancelled.

Claims 3-6 and 19-21 are examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections

Specification

3. The disclosure is no longer objected to because of the following informality: page 10, line 24 a sentence does not end with a period, has been amended to include a period.

Claim Objections

4. The objection of claims 19 and 21 is withdrawn because the claims have been amended to reflect deletion of non-elected claims 7 and 9.

Withdrawn Rejections

Claim Rejections - 35 USC § 112

5. The rejection of claims 3-6 and 19-21 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn. Claims 1 and 2 have been cancelled.

Claim Rejections - 35 USC § 102

6. The rejection of claim 6 under 35 U.S.C. 102(b) as being anticipated by Horiuchi et al. (Molecular Human Reproduction 5(2): 139-145, February 1999) is withdrawn in light of the amendments. Claims 1 and 2 have been cancelled.

7. The rejection of claims 1 and 2 under 35 U.S.C. 102(b) as being anticipated by Poon et al. (J. Clin. Invest. 98(10): 2277-2283, November 1996/ IDS reference, exhibit 9 from Paper number 4) is withdrawn in light of the cancellation of the claims.

Maintained Rejections and New Grounds of Rejection

Claim Rejections - 35 USC § 112

8. The rejection of claims 3-6 and 19-21 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained. Claims 1 and 2 have been cancelled.

Applicants assert the steps required for identifying the chemical compound listed in the claimed methods are of record in the specification and the use of the said compounds is all that is required of the claimed invention. Applicants contend that the method of treatment to a human, based on the teachings of a method of treating a non-human animal, is not a requirement of patentability. These points of view and arguments have been carefully considered and found partially persuasive.

Applicants' assertion regarding the requirement of patentability in the context of non-human animals and humans is true. And while Applicants set forth guidelines in the specification noting identification of compounds the crux of the issue is the unpredictability in the art of administering undefined and uncharacterized compounds for the treatment of cardiovascular disease and cancer. Although there are some compounds such as rapamycin (listed in Applicants' specification) that increase p27 acitivity, thereby alleviating and inhibiting cardiovascular disease and tumor metastasis, respectively the broad genus of compounds listed in the claimed invention can not predictably do the same. For instance, peroxisome proliferators-activated receptor γ (PPAR γ) ligands have been identified as compounds that increase the expression of $p27^{27kip1}$. Accordingly, these compounds have been noted to exhibit anticancer activity, however they stimulate cancer formation as well, see abstract and Table 4 on page 6 of Koeffler (Clinical Cancer Research 9: 1-9, January 2003). This evidence underlines the unpredictability that exists in the art. As stated in the first action on the merits (FAOM) the broadly described molecules may not maintain the activities and function as proposed in the specification. In the absence of an established role of the broad

chemical compounds in targeted treatment of cancer and cardiovascular diseases it is impossible to predict what if any therapeutic effect the administration of any of these molecules would have in the said methodologies. There is insufficient data or established precedent presented that would lead one of skill in the art to believe that the broadly listed compounds would be able to function as the methodology dictates, i.e. inhibiting tumor metastasis. It is clear from the figures that the administration of rapamycin *in vitro* and *in vivo* produced effects such as significant inhibition of smooth muscle cells (SMC) migration, however there is insufficient evidence supporting the broadly listed compounds would yield such a result. The analysis established in this Action, as well as in the FAOM sustains the Examiner's position that there appears to be no nexus between Applicants' broadly claimed method of treating a subject affected with cardiovascular disease and tumor metastasis by administering a broad genus of undefined chemical compounds.

The specification provides insufficient guidance with regard to administering a plethora of compounds, which increase intracellular cyclin-dependent kinase inhibitor p27 activity for the treatment of disorders. The specification also does not present sufficient working examples, which would provide guidance and significant preponderance of predictability to one skilled in the art the use of the said compounds with a reasonable expectation of success. In view of the unpredictability of the art one of skill in the art would be forced into undue experimentation to practice implementation of the claimed invention.

9. Claims 19-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 19 and 21 contain the recitation "under conditions suitable for increasing p27 activity" which is indefinite. It is not clear what conditions are deemed appropriate or conducive to increasing the said activity. Applicants are requested to clarify these conditions.

Claim Rejections - 35 USC § 102

10. The rejection of claims 3-6 and 19-21 under 35 U.S.C. 102(b) as being anticipated by WO 99/65939/ IDS reference from Paper number 8 (23 December 1999) is maintained. Claim 1 has been cancelled.

Applicants argue the "...WO document is directed solely to methods of inhibiting cell proliferation, whereas the subject application provides method for inhibiting cell migration", see Response submitted May 29, 2003, page 18, second paragraph. Applicants note that cell proliferation and cell migration are clearly distinct phenomena and consequently the instant rejection should be withdrawn. Applicants arguments and points of view have been carefully considered but found unpersuasive.

As set forth in the FAOM this WO document discloses methods for modulating, i.e. enhancing the activity of a p27(Kip1).FKBP-12 complex, see page 9, lines 24 and 25. Consequent to the enhancement of this intracellular cyclin-dependent kinase inhibitor p27 activity there is cell cycle arrest and control of physiological processes such as hyperproliferative disorders, atherosclerosis and cardiac and muscle disease,

see page 9, lines 24-32. The role of the cyclin kinase inhibitor p27(Kip1) is clearly implicated in artherosclerosis, tumorigenesis, tumor progression and spread, see page 7, lines 9-11. "p27(Kip1) expression levels correlate with cancer progression since a decrease in p27(Kip1) expression levels significantly correlates with advanced stage, depth of tumor invasion and lymph node metastasis.", see bridging sentence of pages 5 and 6. Tumor spread is art known to be the migration of cancer cells from one site (i.e. part of the body) to another site. The disclosed invention provides a method for treatment or prevention of various diseases and disorders, such as those related to organ transplantation, tumor spread, autoimmune diseases and atherosclerosis by administration of a therapeutic compound that modulates, i.e. promotes p27(Kip1).FKBP-12, see page 27, lines 10-29; page 33, lines 3-5. The administration of these compounds upregulate p27 activity and thereby alleviates cardiovascular disease, inhibits tumor metastasis and inherently increased by increased of C3 exoenzyme activity.

The WO document includes protein-protein interaction assays for assaying and screening derivatives, fragments, analogs and homologs of FKBP-12 for binding to p27(Kip1) in order to detect compounds that increase p27 activity and after the subsequent identification of these compounds they are administered, see page 46, line 30-page 47, line 20; page 48, line 9-page 49, line 15; page 50, line 31-page 53, line 26.

11. The rejection of claims 3-6under 35 U.S.C. 102(b) as being anticipated by WO 99/03508/ IDS reference from Paper number 8 (28 January 1999) is maintained. Claims 1 and 2 have been cancelled.

Applicants argue the Examiner's rejection is directed exclusively to arresting cell growth and the Examiner's conclusion that inhibition of cell growth is concurrent with the prevention of cell migration is incorrect, therefore the rejection should be withdrawn. These points of view and arguments have been carefully considered, but found unpersuasive.

The WO 99/03508 discloses methods for treating and preventing vascular proliferative diseases *in vivo* including restenosis, artherosclerosis and angiogenesis with a mutated p27 or p27 fused with thymidine kinase, see page 4, lines 6-15 and pages 30 and 31, claims 1-16. This WO document also discloses a method for providing a gene composition which expresses p27 in a therapeutically effective amount to a patient with a vascular proliferative disease, such as atherosclerosis, angiogenesis and restenosis, see page 4, lines 7-21; page 10, line 11-page page 12, line 2. Inherent in the treatment of these diseases is the inhibition of cellular migration. The disclosed medicaments upregulate p27 activity. Moreover, inherently the increase/enhancement of the cyclin-dependent kinase inhibitor p27 is due to the increase of C3 exoenzyme activity.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 3-6 and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/03508/ IDS reference from Paper number 8 (28 January 1999), and further in view of WO 99/65939/ IDS reference from Paper number 8 (23 December 1999).

The teachings of the WO document numbered 99/03508 have been presented above. This document does not teach the methodology used to identify the compound that inhibits cellular migration.

However, WO/996539 does teach protein-protein interaction assays for assaying and screening compounds for binding to p27(Kip1) in order to detect compounds that increase p27 activity and after the subsequent identification of these compounds they are administered, see page 46, line 30-page 47, line 20; page 48, line 9-page 49, line 15; page 50, line 31-page 53, line 26. it would have been prima facie obvious at the time the claimed invention was made to implement an assay to quickly and efficiently identify compounds that modulate p27 activity. One of ordinary skill in the art would have been motivated to use the teachings of both documents with a reasonable expectation of success because WO 99/65939 established a screen assay and WO 99/03508 established studies determining the effect of cyclin-dependent kinase inhibitors, Example 5 on pages 24 and 25.

Conclusion

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571)272-0831. The examiner works a flexible schedule, however she can normally be reached between the hours of 6:30 am to 5:30 pm with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

Alana M. Harris, Ph.D.
18 April 2005